

PAEDIATRICS

# Comparison of propofol and fentanyl administered at the end of anaesthesia for prevention of emergence agitation after sevoflurane anaesthesia in children

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## Editor's key points

- Emergence agitation is common in children after sevoflurane anaesthesia.
- This prospective randomized trial compared the use of propofol or fentanyl administered at the end of anaesthesia in reducing emergence agitation.
- Both propofol and fentanyl reduced emergence agitation, but fentanyl was associated with more postoperative nausea and vomiting.

**Background.** Propofol and fentanyl can be administered at the end of sevoflurane anaesthesia to decrease the incidence and severity of emergence agitation (EA), although it has not been determined which agent has superior efficacy. The purpose of this study was to compare the effects of propofol and fentanyl on EA.

**Methods.** In this prospective, randomized, double-blind study, 222 children, 18–72 months of age, undergoing sevoflurane anaesthesia were randomly assigned to one of the three groups receiving either propofol 1 mg kg<sup>-1</sup> (Group P), fentanyl 1 µg kg<sup>-1</sup> (Group F), or saline (Group S) at the end of anaesthesia. The incidence and severity of EA were evaluated with the paediatric anaesthesia emergence delirium (PAED) scale. Time to recovery and incidence of nausea/vomiting were assessed.

**Results.** The mean PAED score was 4.3 in Group P and 4.9 in Group F ( $P=0.682$ ), which were lower than 9.0 in Group S ( $P<0.001$ ). Nausea and vomiting were significantly more frequent in Group F than Groups P and S (adjusted  $P=0.003$  and adjusted  $P<0.001$ ). Group F had also longer stay in the post-anaesthesia care unit (PACU) than Group S ( $P<0.001$ ), while Group P did not. However, the differences in PACU stays between the P and F groups were considered clinically insignificant.

**Conclusion.** Small doses of propofol or fentanyl at the end of sevoflurane anaesthesia comparably reduced EA. Propofol was better than fentanyl due to a lower incidence of nausea and vomiting.

**Keywords:** anaesthetics i.v., propofol; anaesthetics volatile, sevoflurane; analgesics opioid, fentanyl; recovery, postoperative

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Emergence agitation (EA) in children early after sevoflurane anaesthesia is a common postoperative problem, with incidence ranging up to 80%.<sup>1,2</sup> It is characterized by behaviour that can include crying, disorientation, excitation, and delirium. Although EA is self-limiting and might not result in permanent sequelae, it carries the risks of self-injury and is a cause of stress to both caregivers and families.<sup>3,4</sup>

Different strategies have been suggested to decrease the incidence and severity of EA, such as administering sedative medication before induction, a change in the maintenance technique of anaesthesia, or pharmacological agent administration at the end of anaesthesia.<sup>2,5–7</sup> Among these strategies, the use of pharmacological agents at the end of anaesthesia is thought to be the most convenient and easily applicable method in clinical situations, since it does

not rely on the nature of the anaesthetic agents used during induction and maintenance or the duration of anaesthesia.<sup>2,8,9</sup> From this perspective, low doses of propofol or fentanyl (1 mg kg<sup>-1</sup> or 1 µg kg<sup>-1</sup>, respectively) have been shown to successfully reduce EA if administered at the end of anaesthesia.<sup>1,2,10</sup> However, these studies were carried out independently under different conditions with various assessment tools, and the therapeutic efficacies of these two drugs have not been directly compared. In addition, their different molecular mechanisms could influence different variables related to recovery and complications.<sup>1,11</sup> Therefore, we hypothesized that the effects of decreasing the incidence and severity of EA and recovery profiles are different between propofol and fentanyl under comparable clinical conditions.

The purpose of this randomized double-blinded study was to compare the effects of propofol and fentanyl administered at the end of sevoflurane anaesthesia on EA in children undergoing inguinal hernia repair. In addition, characteristics of anaesthesia recovery and incidence of adverse effects were compared.

## Methods

This study was approved by the institutional review board of Severance Hospital, Yonsei University Health system (ref: 4-2010-0536), and was registered with ClinicalTrials.gov (ref: NCT01506622). Written informed consent was obtained from the parents of all participants. Two hundred and twenty-two children, 18–72 months of age, ASA class I or II, who were undergoing ambulatory inguinal hernia repair under general sevoflurane anaesthesia, were prospectively included in this study. Children with developmental delay, psychological or neurological disorders, abnormal airway, reactive airway disease, or history of general anaesthesia were excluded. All patients fasted at least 8 h, with an opportunity to drink clear fluids up to 4 h before operation.

The enrolled children were randomly allocated to one of the three groups to receive either propofol (Group P), fentanyl (Group F), or saline (Group S) in a double-blinded fashion according to random number sequences generated by an Internet site program (<http://www.random.org/>). The agents used for this study were prepared in a 2 ml syringe wrapped in aluminium foil by an investigator who was not involved in the anaesthesia process.

Subjects were not premedicated. Upon arrival at the operating theatre, subjects were monitored by pulse oximetry, capnography, non-invasive arterial pressure, and electrocardiography. Anaesthesia was induced by inhalation of 8% sevoflurane in oxygen via a face mask with monitoring of inhaled and exhaled sevoflurane concentrations. Induction quality was briefly evaluated according to a four-point scale: 1, crying, needs restraint; 2, moderate fear and reassured with difficulty; 3, slight fear but can be reassured easily; and 4, asleep or calm or awake and co-operative, accepting the mask.<sup>5</sup> Subjects presenting with a score of 1 were withdrawn from the study. After the loss of consciousness, sevoflurane was adjusted to end-tidal 3–3.5% and maintained for several minutes and an i.v. cannula was inserted. A laryngeal mask airway (LMA™, The Laryngeal Mask Company Ltd, UK) was inserted after adequate jaw relaxation was attained. LMA size, according to the manufacturer's guidelines, was size 2 for 10–20 kg body weight, size 2.5 for 20–30 kg, and size 3 for 30–50 kg. If LMA insertion failed after three attempts, tracheal intubation was performed and the subject was withdrawn from the study. After LMA insertion and before operation, the subjects received a caudal block with 1.2 ml kg<sup>-1</sup> of 0.5% lidocaine. Skin incision served as the test of adequate analgesia of the caudal block, and the block was deemed inadequate if heart rate increased >20% within 60 s of skin incision. Only subjects with an adequate caudal block were included in this study.

During the operation, anaesthesia was maintained with sevoflurane 2–2.5% in ~50% oxygen with a total inflow of 2 litre min<sup>-1</sup>. Spontaneous ventilation was maintained in all subjects.

About 10 min before completion of surgery, anaesthesia was maintained with 2% sevoflurane with a total inflow of 6 litre min<sup>-1</sup>. At the completion of surgery, the concentration of oxygen was adjusted to 100% while anaesthesia was maintained. At the same time, subjects received propofol 1 mg kg<sup>-1</sup>, fentanyl 1 µg kg<sup>-1</sup>, or saline over 1 min according to the allocated group. The study drug wrapped in foil was injected through a three-way stopcock directly connected to an angiocatheter, so the attending anaesthesiologist and the investigator who collected the data remained blinded to the agent administered. After regular breathing with adequate tidal volume (>6 ml kg<sup>-1</sup>) was confirmed, the LMA was removed under anaesthesia. Sevoflurane was discontinued immediately after removal, 100% oxygen via a face mask was given, and subjects were observed for at least 5 min for the management of possible respiratory complications such as upper airway obstruction, breath holding, or suspicious laryngospasm. When spontaneous breathing with airway patency without assistance was confirmed and complications were resolved, subjects were transferred to the post-anaesthesia care unit (PACU).

Upon arrival at the PACU, subjects were monitored and cared for by two nurses. Guardians were not allowed to stay in the PACU because of the policy of our institute. Three different investigators (one anaesthetist and two nurses) who were blinded to subject allocation evaluated EA and recovery. First, the anaesthetist assessed recovery of consciousness defined as crying or eye opening in response to verbal command or light touch every 5 min from the arrival at the PACU, and recorded the time taken to recover consciousness. The degree of agitation was evaluated and recorded upon awakening and every 5 min thereafter during the first 30 min, and the highest-recorded value was used for evaluation. The anaesthetist evaluated the incidence and severity of EA using the paediatric

**Table 1** The PAED scale. The scores of individual items are summed to produce a total PAED score. The severity of EA increased proportional to the total score

|                                                | Score           |
|------------------------------------------------|-----------------|
| The child makes eye contact with the caregiver | 4=not at all    |
| The child's actions are purposeful             | 3=just a little |
| The children is aware of the surroundings      | 2=quite a bit   |
|                                                | 1=very much     |
|                                                | 0=extremely     |
| The child is restless                          | 0=not at all    |
| The child is inconsolable                      | 1=just a little |
|                                                | 2=quite a bit   |
|                                                | 3=very much     |
|                                                | 4=extremely     |

anaesthesia emergence delirium (PAED) scale (Table 1).<sup>2 12</sup> In addition, Aono's scale (1, calm; 2, easily consoled state; 3, moderate agitation; 4, severe agitation) and the five-step EA scale (1, obtunded with no response to stimulation; 2, asleep but responsive to movement or stimulation; 3, awake and responsive; 4, crying; 5, thrashing behaviour that requires restraint)<sup>13 14</sup> were used to assess EA by two nurses independent of the anaesthesiologist. Aono's scale scores  $\geq 3$ , or five-step EA scale  $\geq 4$  were considered as the presence of EA.<sup>2 12 14</sup> Subjects with an Aono's scale of 3 or higher for more than 5 min were treated with i.v. propofol  $1 \text{ mg kg}^{-1}$  as a rescue medication.

When subjects were fully awake, and had stable vital signs, patent airway without support, and oxygen saturation  $>95\%$  breathing room air, they were transferred to the outpatient recovery room and stayed with their guardian. Subjects were to remain in the outpatient recovery room for at least 3 h before discharge according to the protocol of our institute. During the whole recovery period, the occurrence of nausea or vomiting was assessed and treated with ondansetron  $0.1 \text{ mg kg}^{-1}$ . Nausea was defined as a feeling of the urge to vomit, and vomiting was defined as retching and any expulsion of liquid gastric contents after oral fluid intake. The anaesthetist who assessed PAED scale also recorded the duration of PACU stay, delayed discharge from the outpatient recovery room, adverse events such as somnolence, delayed voiding, and nausea or vomiting.

### Statistical analysis

Previous studies reported the prevalence of EA as  $\sim 10\text{--}20\%$  under effective planned methods. According to power analysis, a sample size of 59 patients per group would have 80% power to detect a difference of 20% at a significance level of 5%, based on the assumption that the prevalence of EA in the more effective of the two drugs would be 10%. Finally, 74 patients were required in each group when considering a drop-out rate of 20%. Continuous variables were reported as mean (sd) and were analysed using the one-way analysis of variance test with *post hoc* multiple comparisons. Categorical data such as the incidence of EA were reported as numbers and percentages and were analysed using the  $\chi^2$  test or Fisher exact test with the Bonferroni correction to calculate adjusted *P*-values. A *P*-value of  $<0.05$  was considered statistically significant.

### Results

Of 265 patients who were initially assessed, 205 patients successfully completed the study (Fig. 1). There were no significant differences in age, weight, gender, or duration of anaesthesia among the three groups (Table 2).

The mean values of PAED score in Group P [4.3 (3.2)] and Group F [4.9 (3.5)] were significantly lower than the value of Group S [9.0 (5.3)] ( $P<0.001$ ), and there was no significant difference between Groups P and F ( $P=0.682$ ) (Fig. 2). Both Aono's scale and five-step EAS also showed that the

incidence of EA in Groups P and F was similar and significantly lower than that in Group S (adjusted  $P<0.001$ ) (Fig. 3).

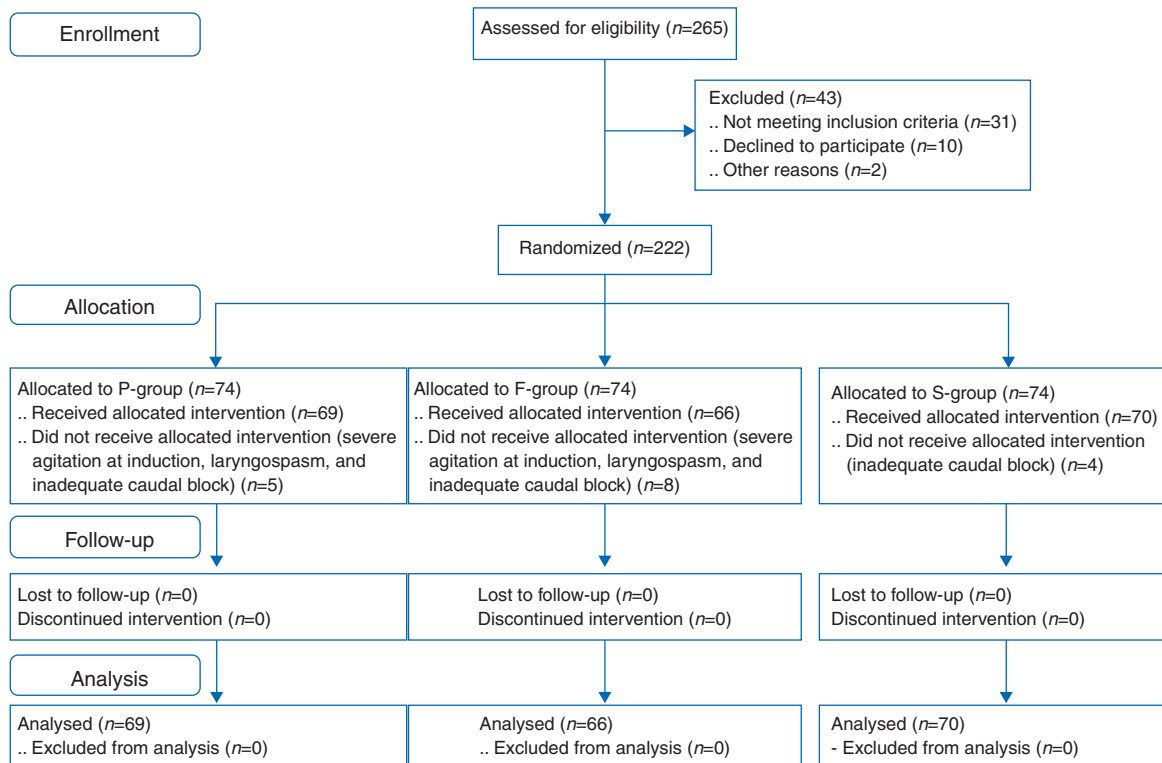
The time for awakening of Groups P and F was comparable ( $P=0.394$ ) and significantly longer than that of Group S ( $P<0.001$ ) (Table 3). Subjects in Group F stayed longer in the PACU [40.4 (11.5) min] than those in Group S [33.4 (10.3) min] ( $P<0.001$ ). However, there was no statistical difference in PACU stay duration between Groups F and P [37.1 (8.7) min] ( $P=0.108$ ) and between Groups P and S ( $P=0.194$ ). All subjects were discharged after 3 h admission in the outpatient recovery room.

Complications are shown in Table 4. Two subjects in Group P and four in Group F required jaw thrust for the maintenance of upper airway patency, and two subjects (one each from Groups P and F) presented with suspicious laryngospasm, which was resolved by continuous positive pressure ventilation. Propofol as rescue medication of EA was more frequently used in Group S compared with the other two groups (adjusted  $P<0.001$ ). The incidence of nausea or vomiting was significantly higher in Group F than in Groups P and S: 26% of subjects in Group F required antiemetic medication (adjusted  $P=0.003$  and adjusted  $P<0.001$ ).

### Discussion

This study revealed that administration of either propofol  $1 \text{ mg kg}^{-1}$  or fentanyl  $1 \mu\text{g kg}^{-1}$  at the end of sevoflurane anaesthesia was comparable in reducing EA compared with saline, and that subjects who received propofol had less vomiting compared with those who received fentanyl. Fentanyl also increased the duration of PACU stay in comparison with saline, while Group P did not. However, the differences in PACU stay duration between Groups P and F were considered clinically insignificant.

Various agents have been investigated with the aim of reducing the occurrence of EA, with variable outcomes. A recent meta-analysis demonstrated that propofol, fentanyl,  $\alpha_2$ -adrenergic receptor agonist, and ketamine have a prophylactic effect.<sup>8</sup> However, the relative efficacy of one drug over others was not clear. Particularly, regarding the drugs administered at the end of anaesthesia, only two recent studies were conducted with the aim of comparing two or three drugs. Chen and colleagues<sup>15</sup> compared the concurrent use of midazolam, propofol, or ketamine with fentanyl just after discontinuing sevoflurane anaesthesia in children who underwent cataract surgery and showed that propofol or midazolam in combination with fentanyl were both effective in reducing EA. However, the effect of propofol or midazolam on EA is additive or synergistic with fentanyl because fentanyl is thought to decrease the incidence and severity of EA independent of its analgesic effect.<sup>10 16</sup> Kim and colleagues also compared propofol and midazolam in patients undergoing strabismus surgery. They similarly found that propofol and midazolam decreased the incidence of EA by about 40%, but the final incidence of EA in the prophylactic groups was 40%, which is higher than the 15–20% of Chen and colleagues' study.<sup>17</sup> Furthermore, both of these studies



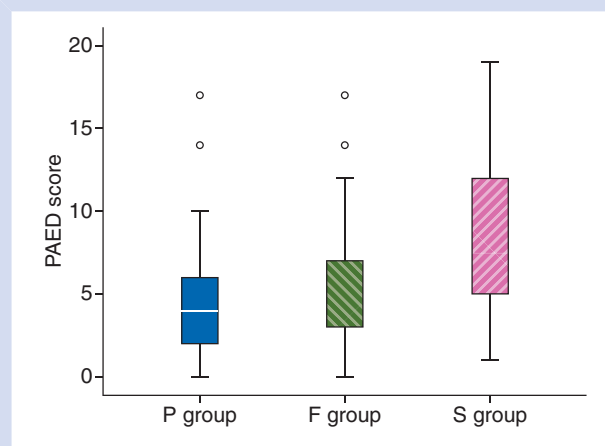
**Fig 1** Consort flow diagram. P, propofol; F, fentanyl; S, saline.

**Table 2** Subject characteristics and duration of anaesthesia. Data are presented as mean (range) for age, mean (sd) for weight, duration of anaesthesia, and number of patients (%). P, propofol; F, fentanyl; S, saline

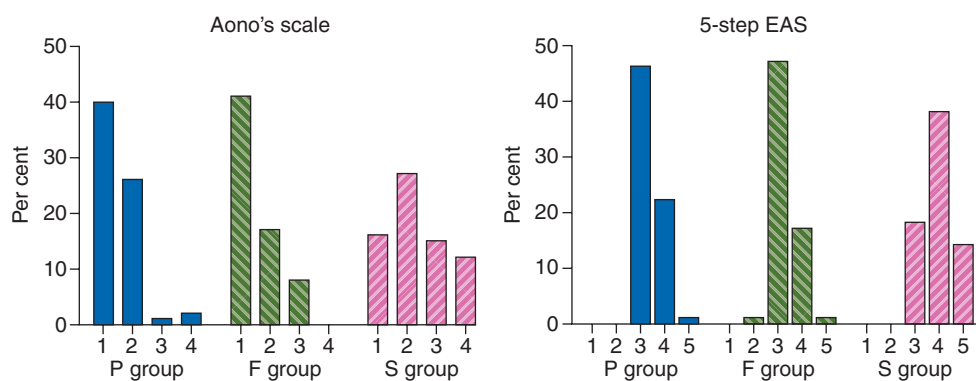
|                               | Group P<br>(n=69) | Group F<br>(n=66) | Group S<br>(n=70) |
|-------------------------------|-------------------|-------------------|-------------------|
| Age (yr)                      | 3.6 (1.8–6.0)     | 3.7 (1.5–6.0)     | 3.8 (1.7–5.9)     |
| Weight (kg)                   | 15.7 (3.3)        | 15.9 (3.6)        | 15.6 (3.0)        |
| Gender (M/F)                  | 52 (75)/17 (25)   | 38 (58)/28 (42)   | 48 (69)/22 (31)   |
| Duration of anaesthesia (min) | 63.5 (14.8)       | 61.6 (11.9)       | 62.1 (11.9)       |

compared propofol and midazolam only in patients undergoing ophthalmological surgery. More comparative studies need to be conducted with additional combinations of drugs and in diverse clinical situations. Hence, we compared propofol and fentanyl, which are most commonly studied in the field of EA, in patients undergoing inguinal hernia repair.

Propofol is frequently used in children for induction and maintenance of general anaesthesia.<sup>18 19</sup> Because of the pharmacokinetic properties of propofol, anaesthesia maintenance rather than induction provides a smoother recovery profile in children compared with that of sevoflurane.<sup>6 8 20</sup>



**Fig 2** Distributions of the PAED score. PAED, paediatric anaesthesia emergence delirium; P, propofol; F, fentanyl; S, saline. The box contains the middle 50% of the data. The upper edge of the box indicates the 75th percentile of the data set, and the lower edge indicates the 25th percentile. The range of the middle two quartiles is known as the inter-quartile range. The ends of the vertical lines indicate the minimum and maximum data values, unless outliers are present in which case the vertical lines extend to a maximum of 1.5 times the inter-quartile range. Any data not included between the vertical lines are plotted as an outlier with a circle.



**Fig 3** Distributions of scores according to Aono's scale and the five-step EAS. EAS, emergence agitation scale; P, propofol; F, fentanyl; S, saline. Aono's scale (1, calm; 2, easily consoled state; 3, moderate agitation; 4, severe agitation) and five-step EA scale (1, obtunded with no response to stimulation; 2, asleep but responsive to movement or stimulation; 3, awake and responsive; 4, crying; 5, thrashing behaviour that requires restraint).

**Table 3** Comparison of time for awakening and PACU stay duration among the three groups. PACU, post-anaesthesia care unit; P, propofol; F, fentanyl; S, saline; Time for awakening, time period from administration of study agent to emergence; PACU duration, time period from admission to discharge from PACU. \*The time for awakening of Groups P and F was comparable ( $P=0.394$ ) and significantly longer than that of Group S ( $P<0.001$ ). †There were no significant differences of the PACU duration between Groups P and S ( $P=0.108$ ). ‡There were no significant differences of the PACU duration between Groups P and F ( $P=0.194$ ). §The PACU duration of Group F was significantly longer than that of Group S ( $P<0.001$ ).

|                          | Group P<br>(n=69)         | Group F<br>(n=66)          | Group S<br>(n=70)           |
|--------------------------|---------------------------|----------------------------|-----------------------------|
| Time for awakening (min) | 27.7 (8.5)*               | 30.5 (12.3)*               | 17.6 (11.9)*                |
| PACU duration (min)      | 37.1 (8.7) <sup>†,‡</sup> | 40.4 (11.5) <sup>†,§</sup> | 33.4 (10.3) <sup>†,  </sup> |

**Table 4** Incidence of complications and use of rescue medications during the postoperative period. There were no significant differences in incidences of airway obstruction, laryngospasm, and delayed voiding among the three groups. \*The incidence of nausea or vomiting and the use of ondansetron in Group F were significantly higher than those in Groups P and S (adjusted  $P=0.003$  and adjusted  $P<0.001$ ). †The incidence of rescue propofol use in Group S was significantly higher than those in the other two groups (adjusted  $P<0.001$ ). P, propofol; F, fentanyl; S, saline

|                    | Group P<br>(n=69)    | Group F<br>(n=66)  | Group S<br>(n=70)      |
|--------------------|----------------------|--------------------|------------------------|
| Airway obstruction | 2 (2.9)              | 4 (6.0)            | 0 (0)                  |
| Laryngospasm       | 1 (1)                | 1 (2)              | 0 (0)                  |
| Nausea or vomiting | 4 (5.8)*             | 17 (25.8)*         | 2 (2.9)*               |
| Delayed voiding    | 0                    | 0                  | 1 (1.4)                |
| Propofol use       | 1 (1.4) <sup>†</sup> | 0 (0) <sup>†</sup> | 17 (24.3) <sup>†</sup> |
| Ondansetron use    | 4 (5.8)*             | 17 (25.8)*         | 2 (2.9)*               |

However, induction is commonly achieved without intravascular access in paediatric anaesthesia.<sup>21</sup> Fortunately, several studies have suggested that a single administration of  $1 \text{ mg kg}^{-1}$  of propofol at the discontinuation of anaesthesia is effective in reducing EA without delay of discharge from the PACU in children receiving sevoflurane for induction and maintenance of anaesthesia.<sup>1, 2</sup> In the above studies, children underwent strabismus surgery or magnetic resonance imaging. Fentanyl provides another option at discontinuation of anaesthesia. One previous study evaluated the effect of fentanyl on EA with a dose smaller than that used for induction ( $1 \mu\text{g kg}^{-1}$ ) in children after sevoflurane anaesthesia without surgery; the incidence of EA was decreased independent of its analgesic effects, and the time to achieve hospital discharge criteria was not prolonged.<sup>10</sup> Therefore,

although the analgesic properties of fentanyl play a role in decreasing the incidence and severity of EA, supplementation of sevoflurane anaesthesia with a small dose of fentanyl can also be considered even in the absence of substantial postoperative pain. The present study was conducted to compare the efficacies of these two drugs in decreasing the incidence and severity of EA under the same clinical condition, which has not been previously performed. According to our results, there were no differences in efficacy between propofol and fentanyl in decreasing the incidence and severity of EA after sevoflurane anaesthesia.

Drug selection for a specific purpose is based not only on efficacy, but also on possible complications or side-effects.



We found that the incidence of nausea or vomiting in the fentanyl group was 26%, which was much higher than that of Group P, despite comparable efficacies of the two drugs in decreasing the incidence and severity of EA. In a previous study conducted to estimate the mean effective dose of fentanyl required for the reduction in EA, postoperative vomiting also occurred in 75% of patients.<sup>22</sup> Although the incidence of postoperative vomiting of the present study did not lead to delayed discharge because all patients remain in the outpatient recovery room for at least 3 h according to the policy of our institute, the risk of emesis should be considered when fentanyl is used for prophylaxis of EA. Another concern for using propofol and fentanyl at the end of anaesthesia is the possibility of delayed emergence. Both propofol and fentanyl delayed the time taken for awakening more than 10 min than placebo. However, the children in Groups P and F were transferred to the outpatient recovery room from the PACU after 10 min upon their awakening, whereas the children in Group S took more than 15 min for discharge from the PACU. Therefore, slightly delayed awakening after propofol or fentanyl administration might not lead to clinically significant delayed discharge from the PACU.

Although EA after sevoflurane anaesthesia can occur in pain-free patients, postoperative pain is also a well-known cause of postoperative distress and agitation in children. In consequence, the effects of anaesthetic techniques on EA should ideally be investigated in the absence of post-surgical pain.<sup>10 23 24</sup> In our study, a caudal block was performed for postoperative analgesia and also to exclude any contribution of postoperative pain to the occurrence of EA. Some previous studies proposed that a preoperative caudal block in children after sevoflurane anaesthesia is effective in decreasing the incidence and severity of EA, and that the incidence of EA in patients with caudal block varied from 4.5% to 26%.<sup>21 23</sup> The lower incidence of EA in previous studies than that of Group S in the present study might be due to the use of midazolam as premedication and parental presence in the PACU which were not used in our study.<sup>21 23</sup>

A reliable scale or scoring system to assess whether EA is present should be used for the objective comparison of two drugs. The PAED scale used preferentially for assessing EA in this study is a typical evaluation tool of EA, and its reliability and validity have been supported by companion papers.<sup>12 25</sup> However, previous studies used other scales besides the PAED scale, and the incidence of EA might be different depending on the evaluation tools.<sup>8 14</sup> Therefore, we used not only the PAED scale but also the two additional scales, and propofol and fentanyl showed comparable efficacy in the prevention of EA by all three scales.

Our study has several limitations. First, we investigated only children with inguinal hernia repair. The incidence of EA is different depending on the type of surgery and is known to be higher in otorhinolaryngological or ophthalmological procedures,<sup>26</sup> suggesting that the efficacy of propofol and fentanyl in the present study might be modified in different types of surgical procedures. However, by limiting the type of surgery, we could perform the distinct comparison

of the two agents with the elimination of the surgical effects on EA. Secondly, children with severe preoperative anxiety were excluded from this study. Preoperative anxiety has been proposed to promote and exacerbate EA,<sup>21 27</sup> so additional study of effects of propofol and fentanyl on EA in these patients might be clinically beneficial. Thirdly, the lack of follow-up after discharge could be considered as a limiting factor in the interpretation of these study results because there may be late onset nausea or vomiting.<sup>28 29</sup> In spite of this, the statistically significant difference of between propofol and fentanyl (5.8% vs 25.8%) in the frequency of nausea or vomiting during the recovery period allowed us to confirm the advantage of propofol in relation to nausea or vomiting. Lastly, the 3 h stay at the outpatient recovery room, which is the routine protocol of our institute, might have failed to discriminate a difference in discharge time between the three groups.

In summary, the use of either propofol or fentanyl at the discontinuation of sevoflurane anaesthesia effectively reduced the incidence of EA, and propofol might be preferable regarding the lower incidence of vomiting.

## Declaration of interest

None declared.

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